Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease

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Genetic determinants of ulcerative colitis include the *ECM1* locus and five loci implicated in Crohn's disease

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AUTHOR CONTRIBUTIONS

S.A.F., M.T., C.A.A., C.G.M., M.P. and J.S. wrote the paper; S.A.F., C.A.A., C.B., J.C.B., C.M.L. and L.C. did statistical analysis; N.J.P., S.B., K.B., M.I., P.E., R.R., D.M., M.T., A.K., S.H. and R.G. performed DNA analysis; N.W. and W.O. supplied control DNA; E.R.N., D.M., M.T., C.J., F.R.C., H.D., C.W.L., C.M.O., C.E.H. and M.C. recruited and phenotyped ulcerative colitis cases; P.D., A.L., A.F., J.S., D.P.J., J.C.M., C.G.M., M.P., the WTCCC and J.S. supervised collections and/or laboratory studies.

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Abstract

We report results of a nonsynonymous SNP scan for ulcerative colitis and identify a previously unknown susceptibility locus at *ECM1*. We also show that several risk loci are common to ulcerative colitis and Crohn's disease (*IL23R, IL12B, HLA, NKX2-3* and *MST1*), whereas autophagy genes *ATG16L1* and *IRGM*, along with *NOD2* (also known as *CARD15*), are specific for Crohn's disease. These data provide the first detailed illustration of the genetic relationship between these common inflammatory bowel diseases.

Ulcerative colitis and Crohn's disease are debilitating inflammatory bowel diseases (IBDs) affecting 1 in 250 individuals of Northern European ancestry. Genetic epidemiological data suggest that they share some but not all susceptibility loci. *NOD2*, identified in 2001, is specific to Crohn's disease. Recently, we and others used genome-wide association scans (GWAS) to identify at least ten more loci confirmed to be associated with risk of Crohn's disease (reviewed in ref. 1).

We now present the first nonsynonymous SNP (nsSNP) scan in ulcerative colitis. We used a staged experimental design. Our discovery cohort of 905 ulcerative colitis cases and 1,465 controls (panel 1) were genotyped using an array custom-made for the Welcome Trust Case Control Consortium (WTCCC; **Supplementary Methods** online)2. After removing poorly performing samples and markers, we analyzed 10,886 nsSNPs and MHC tag SNPs (**Supplementary Methods** and **Supplementary Figs**. 1-3 online). We found 33 markers from 21 distinct loci associated at $P < 0.001$. These were then genotyped in another 936 ulcerative colitis cases and 1,470 control subjects (panel 2; statistics on all cases and controls summarized in Supplementary Table 1 online). Five SNPs from three loci replicated (Table 1 and Supplementary Table 2 online). Finally, we tested 16 SNPs tagging 13 known Crohn's disease-associated loci for association with ulcerative colitis (Table 2 and Supplementary Table 3 online)1.

Of loci not previously associated with IBD, the strongest association in panel 1 was at two nsSNPs in *ECM1* on chromosome 1q21.2 ($P = 1.3 \times 10^{-4}$ at rs3737240; $P = 2.6 \times 10^{-4}$ at rs13294). As this was the strongest new signal, we genotyped these markers in panel 2 and in another independent cohort of 1,146 cases and 1,559 controls (panel 3), and we observed support for the association in both (Table 1). After combining all three panels (2,987 cases and 4,494 controls), association at rs3737240 was significant at $P = 2.3 \times 10^{-6}$ and rs13294 at $P = 7.9 \times 10^{-6}$. The result at rs3737240 withstands Bonferroni correction for 10,886 markers (threshold for significance $P < 4 \times 10^{-6}$) and meets suggested significance levels of $P < 10^{-4}$ to $P < 10^{-6}$ for gene-centric studies2,3. Association at *ECM1* may be specific to ulcerative colitis, as this region was not associated with Crohn's disease in the WTCCC scan4.

The *ECM1* locus, delimited by recombination hotspots, spans 290 kb and includes *MRPS21, PRPF3* and *TARS2*. nsSNPs in flanking blocks showed no association. In additional mapping experiments, we genotyped seven SNPs that fully tag *ECM1* in 1,841 cases (from panels 1 and 2) and 1,470 controls (panel 2), with rs11205387 and rs11810419 showing association with ulcerative colitis (Supplementary Table 4 online). Conditional regression analysis showed that neither nsSNP in *ECM1* fully explained the association. Fine mapping will identify whether the causal variant maps within *ECM1* or elsewhere in this haplotype

block. However, *ECM1* is a plausible candidate gene for ulcerative colitis: it encodes extracellular matrix protein 1, a glycoprotein expressed in small and large intestine, and it interacts with the basement membrane and inhibits matrix metalloproteinase 9 (ref. 5). Notably, ECM1 strongly activates NF-κB signaling6, a key immune regulator. Expression is upregulated in colorectal cancer and metastases, implicating ECM1 in epithelial-stromal interaction5. rs3737240 and rs13294 encode substitutions T130M and G290S: Thr130, residing within a collagen IV binding domain, is conserved in primates and pigs but not rodents, whereas Gly290 is not conserved. Of note, the WTCCC observed modest association between these *ECM1* SNPs and ankylosing spondylitis, a related inflammatory disorder ($P = 0.0041$ and 0.0044, respectively)4.

Replicating earlier findings7, multiple MHC markers showed strong association with ulcerative colitis in panel 1 (Supplementary Fig. 4 online). Association peaked around rs6927022 ($P = 4.7 \times 10^{-8}$) in a 400-kb haplotype block containing *BTNL2* and the HLA loci *HLA-DQA1, HLA-DRA, HLA-DRB5* and *HLA-DRB1*, and was independently replicated (Table 1; rs6927022 could not be genotyped in panel 2 for technical reasons). Previous reports confirmed association between *HLA-DRB1* and ulcerative colitis7,8 but did not resolve whether the causal variant lay within this or a neighboring haplotype block. Our high marker density and large panel size successfully resolved this issue: distal to the recombination hotspots, association diminished substantially, indicating that the causal variant does indeed map to this block.

Resolving the causal variant within this block is hindered by tight linkage disequilibrium (LD). Association between *BTNL2* variants and ulcerative colitis in Japanese populations was explained by LD with *HLA-DRB1**1502 (ref. 9). We stratified *BTNL2* genotypes by *DRB1**1502 status: clear residual association with *BTNL2* ($P = 0.0036$ at rs9268480) suggests contribution of this gene or another in LD with it. *DRB1**0103 was previously associated with ulcerative colitis, especially severe disease[7,8]. Whether this rare allele accounts for the signal we observed awaits formal HLA genotyping.

To clarify genetic correlations between ulcerative colitis and Crohn's disease, we partitioned WTCCC Crohn's disease cases into colonic-only ($n = 501$) and ileal-only ($n = 534$) subphenotypes, and implemented a 'within-cases' test of association on the GWAS data (**Supplementary Methods**). We found that multiple HLA markers within the 400-kb block identified in our ulcerative colitis scan were significantly associated with colonic Crohn's disease, peaking at rs3129872 ($P = 6.8 \times 10^{-9}$, *HLA-DRA*). This corroborates previous association between *HLA-DRB1**0103 and colonic Crohn's disease10 and refines the signal to this haplotype block. Compared to healthy controls (MAF = 0.292), the allele frequency at rs3129872 was significantly elevated in colonic Crohn's disease cases ($P = 4.8 \times 10^{-4}$, MAF = 0.347) and reduced in ileal cases ($P = 5.18 \times 10^{-5}$, MAF = 0.231). We nominally replicated this association ($P = 9.7 \times 10^{-3}$) in our smaller Crohn's disease replication cohort (Supplementary Table 5 online). Thus, determinants within this haplotype block both increase risk of ulcerative colitis and colon-only Crohn's disease and decrease risk of small bowel Crohn's disease. This suggests shared pathogenic mechanisms for colonic forms of IBD distinct from small bowel inflammation.

The third replicable locus detected in the nsSNP scan was *MST1* on chromosome 3p21, a region also associated with Crohn's disease4,11. nsSNP rs3197999 ($P_{\text{panel 1+2}} = 6.0 \times 10^{-6}$; Table 1) results in amino acid change R689C. We subsequently genotyped 20 SNPs tagging the *MST1* locus and seven nsSNPs from surrounding genes with MAF > 0.02, capturing ($r^2 > 0.8$) 70/73 Hapmap SNPs from the 193-kb haplotype block encompassing this locus and 86/93 and 122/136 HapMap SNPs from the 301-kb and 279-kb flanking blocks, respectively. Association peaked at *MST1* (Supplementary Table 4). Conditional regression

analysis showed a marginally significant haplotype effect with rs34823813 and rs9853352. The latter two SNPs in *RNF123* and *IHPK1* are within the same haplotype block as *MST1* and are in strong LD ($r^2 = 0.95$). Although their contribution to ulcerative colitis risk cannot be excluded, the evidence more strongly implicates nsSNP rs3197999 as causal or in strong LD with the causal variant at this locus. Arg689 is strongly conserved in mammals, and MST1 is known to suppress cell-mediated immunity by down-regulating IL-12 (ref. 12).

Finally, we genotyped 16 SNPs tagging 13 Crohn's disease-associated loci identified by GWAS1 in 1,841 ulcerative colitis cases (panels 1 and 2) and 1,470 controls (panel 2). Previous smaller studies, including our own using a panel partially overlapping with the current dataset (**Supplementary Methods**), had identified modest association between ulcerative colitis and *IL23R* variants13,14. Here this association was confirmed ($P = 1.3 \times 10^{-5}$ at rs11805303) (Table 2 and Supplementary Table 3) and refined by genotyping five additional *IL23R* SNPs. In contrast to earlier reports13,14, in ulcerative colitis, but consistent with findings in Crohn's disease14, conditional regression analysis in our large ulcerative colitis panel demonstrated that rs11209026 (R381G) provided the strongest signal ($P = 8.9 \times 10^{-8}$, OR = 0.53), with evidence that additional independent variants also contribute to ulcerative colitis risk (Supplementary Table 4). Association was also observed at rs6556416 in *IL12B* ($P = 6.8 \times 10^{-4}$), which encodes a subunit shared by IL-12 and IL-23 (Table 2). Thus, the Th17 pathway seems as relevant to ulcerative colitis as to Crohn's disease13,14, ankylosing spondylitis2 and psoriasis15.

Among other Crohn's disease-associated loci, association with ulcerative colitis was also seen for the transcription factor gene *NKX2-3* (for rs10883365, $P = 3.3 \times 10^{-4}$ in the ulcerative colitis panel and $P = 2.4 \times 10^{-6}$ using the expanded WTCCC control panel; Table 2). Thus, *NKX2-3* represents another generic IBD locus. However, no association with ulcerative colitis was seen at *IRGM* ($P = 0.72$), *PTPN2* ($P = 0.17$), *ATG16L1* ($P = 0.11$) or the chromosome 5p13 gene desert ($P = 0.19$), despite 80% power to detect an allelic OR = 1.15 with MAF = 0.17 at $P = 0.05$ (*PTPN2* effect in Crohn's disease) and >95% power for OR = 1.36 with MAF = 0.12 at $P = 0.0001$ (comparable to *IRGM* and *ATG16L1* in Crohn's disease).

Several Crohn's disease-associated loci, including the *MST1* locus and variants in the IL-23 pathway, evidently also contribute to ulcerative colitis susceptibility. However, some are disease-specific. Notably, genes associated with Crohn's disease but not ulcerative colitis, including *NOD2* and autophagy genes *ATG16L1* and *IRGM*, affect intracellular handling of bacterial antigens, suggesting distinct pathogenic mechanisms relating to microbial processing. Additional susceptibility loci have yet to be identified, and the scene is set for GWA scans for ulcerative colitis. However, in identifying a previously unknown ulcerative colitis–associated locus at *ECM1* and defining the extent of its overlap with Crohn's disease-associated loci, we have made substantial progress both in understanding the key pathogenic pathways for ulcerative colitis and in illuminating the genetic relationship between these two forms of inflammatory bowel disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of results at SNPs showing replicated association with ulcerative colitis by Cochran-Armitage trend tests

				UC discovery scan (panel 1)			
Marker	**Chr.**	**Position**	**Gene**	**Cntrl MAF**	**UC MAF**	P_{unadj}	P_{GC}
rs3737240	1	148749979	*ECM1*	37.7	43.5	1.3×10^{-4}	4.5×10^{-4}
rs13294	1	148751611	*ECM1*	38.5	44.0	2.7×10^{-4}	7.1×10^{-4}
rs3197999	3	49696536	*MST1*	27.4	32.3	4.1×10^{-4}	0.0010
rs9268480	6	32471822	*BTNL2*	30.9	26.2	6.2×10^{-4}	0.0015
rs660895	6	32685358	*HLA-DRB1*	23.1	17.3	3.1×10^{-6}	1.5×10^{-5}

				UC replication study 1 (panel 2)				
Marker	**Chr.**	**Position**	**Gene**	**Cntrl MAF**	**UC MAF**	***P***	OR_{het} **(95 % CI)**	OR_{hom} **(95% CI)**
rs3737240	1	148749979	*ECM1*	38.4	41.9	0.013	1.08 (0.90,1.29)	1.39 (1.09,1.39)
rs13294	1	148751611	*ECM1*	38.9	42.2	0.020	1.06 (0.88,1.27)	1.36 (1.07,1.73)
rs3197999	3	49696536	*MST1*	28.0	31.9	0.0061	1.16 (0.98,1.38)	1.45 (1.10,1.91)
rs9268480	6	32471822	*BTNL2*	29.9	26.0	0.0064	0.71 (0.60,0.84)	0.86 (0.63,1.16)
rs660895	6	32685358	*HLA-DRB1*	20.2	16.5	0.0035	0.73 (0.60,0.87)	0.79 (0.52,1.12)

				UC replication study 2 (panel 3)			Combined analysis
Marker	**Chr.**	**Position**	**Gene**	**Cntrl MAF**	**UC MAF**	***P***	***P*** [a]
rs3737240	1	148749979	*ECM1*	38.1	41.0	0.038	2.3×10^{-6} [a]
rs13294	1	148751611	*ECM1*	39.6	42.2	0.060	7.9×10^{-6} [a]
rs3197999	3	49696536	*MST1*	-	-	-	8.0×10^{-6}
rs9268480	6	32471822	*BTNL2*	-	-	-	7.2×10^{-6}
rs660895	6	32685358	*HLA-DRB1*	-	-	-	2.8×10^{-8}

Table shows SNPs with $P < 0.001$ in nsSNP scan in panel 1 (905 ulcerative colitis cases and 1,465 controls) and $P < 0.05$ in panel 2 (936 ulcerative colitis cases and 1,470 controls). Odds ratios are given for the minor allele.

P_{GC} = *P* value after adjustment for genomic control inflation factor $\lambda = 1.16$. OR_{het} and OR_{hom} define odds ratios for heterozygotes and homozygotes, respectively.

[a] For markers in *ECM1*, the combined analysis includes the second independent replication study conducted using panel 3 (1,146 ulcerative colitis cases and 1,559 controls). P_{unadj} = unadjusted *P* value from Cochran-Armitage trend test.

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Table 2

Association study results for SNPs previously associated with Crohn's disease in the WTCCC study in 1,841 ulcerative colitis cases and 1,470 controls

				Index association analysis			Combined analysis[a]			
Marker	**Chr.**	**Location**	**Gene or region**	**Control MAF**	**UC MAF**	***P***	**WTCCC control MAF**	***P***	**OR_{het} (95% CI)**	**OR_{hom} (95% CI)**
rs11805303	1p31	67448104	*IL23R*	29.5	34.5	1.3×10^{-5}	31.7	2.2×10^{-4}	1.24 (1.10,1.39)	1.29 (1.07,1.55)
rs12035082	1q24	171165000	Gene desert	40.4	40.5	0.99	38.9	0.26	1.04 (0.92,1.18)	1.10 (0.93,1.31)
rs10210302	2q37	233823578	*ATG16L1*	46.3	48.2	0.061	48.1	0.061	0.96 (0.84,1.10)	0.85 (0.73,1.00)
rs9858542	3p21	49676987	*MST1*	28.8	32.9	6.4×10^{-4}	28.2	1.3×10^{-6}	1.09 (0.97,1.23)	1.71 (1.42,2.06)
rs17234657	5p13	40437266	Gene desert	13.1	13.6	0.39	12.5	0.16	1.09 (0.96,1.25)	1.15 (0.75,1.77)
rs9292777	5p13	40473705	Gene desert	40.0	37.2	0.016	39.4	0.014	0.90 (0.79,1.01)	0.82 (0.69,0.97)
rs10067603[b]	5q23	131831767	*IBD5*	22.2	22.0	0.98	-	0.98	1.05 (0.90,1.22)	0.85 (0.62,1.18)
rs13361189	5q33	150203580	*IRGM*	8.4	7.8	0.30	6.7	0.38	1.00 (0.85,1.17)	2.40 (1.18,4.86)
rs4958847	5q33	150219780	*IRGM*	13.0	11.6	0.096	11.3	0.68	0.90 (0.78,1.04)	1.42 (0.93,2.16)
rs6556416[b]	5q33	158751323	*IL12B*	32.4	28.6	6.8×10^{-4}	-	6.8×10^{-4}	0.84 (0.73,0.97)	0.68 (0.53,0.87)
rs6887695	5q33	158755223	*IL12B*	31.5	34.7	0.0040	31.8	0.0016	1.08 (0.96,1.22)	1.38 (1.15,1.67)
rs7753394	6q23	138126941	*TNFAIP3*	49.8	50.4	0.61	48.2	0.097	1.03 (0.90,1.19)	1.14 (0.98,1.34)
rs10761659	10q21	64115570	Gene desert	45.6	42.7	0.023	46.1	0.0012	0.89 (0.78,1.00)	0.77 (0.66,0.90)
rs10883365	10q24	101277754	*NKX2-3*	48.3	52.6	3.3×10^{-4}	47.7	2.4×10^{-6}	1.20 (1.05,1.38)	1.47 (1.25,1.72)
rs2542151	18p11	12769947	*PTPN2*	16.6	17.5	0.38	16.3	0.14	1.11 (0.98,1.25)	1.06 (0.75,1.49)
rs2836754	21q22	39213610	*FLJ45139*	36.1	36.6	0.56	35.3	0.30	1.13 (1.00,1.27)	1.03 (0.86,1.23)

The combined analysis includes data from 2,938 independent WTCCC controls.

[a] Combined analysis from pooling our control genotypes with WTCCC control data (total 4,408 controls).

[b] rs10067603 was selected as a proxy for SNP rs10077785; rs6556416 is a proxy for rs10045431. No WTCCC control data were available for these SNPs; final *P* values and odds ratios were derived from 1,841 ulcerative colitis cases and 1,470 controls in the replication panel. OR_{het} and OR_{hom} define odds ratios for heterozygotes and homozygotes, respectively.